REMARKS

The Office action dated August 11, 2003 is acknowledged. According to the Office action, claims 1, 3-9 and 11-18 have been rejected as being unpatentable over U.S. 4,954,343 ('343) in view of any of U.S. 5,683,711 ('711) or WO 97/23227 ('227). The Examiner states that claim 1 defines a transdermal therapeutic system ("TTS") comprising a backing layer, a protective release liner and a reservoir. The Examiner describes the reservoir as comprising a polyacrylate adhesive, and an amino group containing a polymer selected from polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines. The Office action describes U.S. '343 as disclosing dermal pharmaceutical preparation comprising acrylic adhesives and a copolymer having an amino group to maintain the drug in a dissolved state without undergoing crystallization. It is acknowledged in the Office action that U.S. '343 does not teach the presence of the drug in the supersaturated state or the particular amino group, but says that the disclosure of the genus makes the selected species not patentable.

Further, the Office action describes WO '227 as teaching a transdermal patch with a backing layer, a protective release liner, and a pressure sensitive matrix layer having a drug and a crystallization inhibitor. The matrix layer is said to be acrylate copolymers and includes the drug oestradiol and norethisterone ("NETA") in a supersaturated state.

The Examiner concludes that it would have been obvious to provide a reservoir of acrylate adhesive comprising a high concentration of oestradiol and NETA, and the amino group of U.S. '343. The Examiner's position goes on to state that the high concentration of hormones by supersaturated state of hormones as disclosed in the two cited references, motivated by the teaching of U.S. '711 that supersaturation is necessary to impart a high thermodynamic activity to the drugs,

or motivated by WO '227 that the patch of oestradiol and NETA in a supersaturated state in the copolymeric matrix confers activity to the active ingredients for forced diffusion through the skin.

However, it is respectively submitted that once the important features of the present invention are appreciated, the application in its present form should be allowed. The present invention has a reservoir supersaturated with active ingredients containing oestradiol and norethisterone, attached to a backing layer which was prepared by mixing polyacrylate, pressure sensitive adhesives not comprising amino groups and crystallization inhibitors, the crystallization inhibitor is an amino group-containing polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines, for improving the solubility of the active ingredients.

As explained below, one skilled in the art would not have considered substituting a polyacrylate pressure-sensitive adhesive having an amino group (as taught by the prior art) with one not having an amino group (as claimed in the present application), and mixing it with a polymer selected from the amino-group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines. Most importantly, U.S. '343 and U.S. '711 do not teach or suggest the mixing of a pressure-sensitive adhesive not having amino groups and another amino group-containing polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines. These references also do not teach mixing amino group-containing polymer and a pressure-sensitive adhesive polyacrylate without amino groups for inhibiting crystallization of supersaturated drugs dissolved therein. Likewise, as explained below, WO '227 used a different crystallization inhibitor for oestradiol and/or a progesterone agent, namely octyldecanol which is not a polymer nor contains an amino group.

In order to more precisely define the invention, claims 1 and 15 have been amended to state that the polyacrylate pressure-sensitive adhesive does not comprise amino groups, and claims 1, 15 and 18 have been amended to say that the amino group-containing polymer of the crystallization inhibitor improves the solubility of the active ingredients containing oestradiol and norethisterone. Independent claim 15 has further been amended to describe the hydrogen bonds created between one basic group of the at least one amino group-containing crystallization inhibitor and mobile hydrogen atoms to reduce the concentration of freely mobile oestradiol.

The Examiner states that U.S. '343 teaches a dermal pharmaceutical composition comprising a pressure-sensitive adhesive comprising acrylic adhesives. The acrylic adhesive, inherently, consists of carbon, hydrogen and oxygen. The dermal preparation further comprising copolymer having an amino group. The preparation exhibits excellent adhesion to the skin and remains the drug in a dissolved state. But this is not exactly what U.S. '343 discloses. U.S. '343 teaches a dermal preparation comprising a pressure-sensitive adhesive, wherein said pressure-sensitive adhesive is a copolymer comprising a (meth)acrylamide as comonomer unit (abstract; col. 1, lines 37-43; claim 1). (Meth)acrylamide has an amino group. The preferred main comonomer of the pressure-sensitive adhesive is an alkyl (meth)acrylate (col. 2, lines 22-37). Said alkl (meth)acrylates consist of carbon, hydrogen and oxygen. However, the Examiner overlooked that the pressure-sensitive adhesive does not consist of an alkyl (meth)acrylate, but is a copolymer of said alkyl (meth)acrylate and a (meth)acrylamide. Copolymer means that alkyl (meth)acrylate monomers and (meth)acrylamide monomers are mixed with each other to homogeneity and then are polymerized. Hence, the resulting pressure-sensitive adhesive that can still be considered to be a polyacrylate consists of carbon, hydrogen, oxygen and nitrogen. Apparently, the pressure-sensitive adhesive pursuant to U.S. '343 consists of a single polyacrylate copolymer that consists of carbon, hydrogen,

oxygen and nitrogen. The drug-containing pressure-sensitive adhesive layer does not comprise further copolymers having an amino group.

In contradistinction to the pressure-sensitive adhesive pursuant of U.S. '343 the subject matter of the present invention is a mixture of two polymers, of a polyacrylate pressure-sensitive adhesive that does not contain nitrogen (and hence does not contain amino groups) and an amino group-containing polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines. It should be noted that (meth)acrylamide are not contained in the list of amino group-containing polymers. Pressure-sensitive polyacrylate copolymers having amino groups such as those of U.S. '343 are not comprised by the wording of pending claim 1.

The pressure-sensitive adhesive pursuant to U.S. '343 exhibits good adhesion to the skin. In addition, the polyacrylic pressure-sensitive adhesive comprising a (meth)acrylamide having an amino group as comonomer unit possesses increased polarity as a whole due to the amino linkage (col. 4, lines 51-56). Therefore even hydrophilic drugs can be dissolved in said adhesive in high concentrations without undergoing crystallization (col. 4, lines 56-58). Thus, U.S. '343 teaches that the increased polarity of the amino group-containing polyacrylate is the active principle that is responsible for keeping the drug in a dissolved state and increasing the capacity at which a drug can be dissolved in said polyacrylate pressure-sensitive adhesives, i.e. more drug can be dissolved in the polyacrylate pressure-sensitive adhesive comprising a (meth)acrylamide having an amino group as comonomer than in a polyacrylate pressure-sensitive adhesive not comprising a (meth)acrylamide having an amino group as comonomer

U.S. '343 does not provide any hint to the skilled artisan that replacing the polyacrylate pressure-sensitive adhesive comprising a (meth)acrylamide having an amino group as comonomer

with a mixture of a polyacrylate pressure-sensitive adhesive not comprising amino groups and a polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines would improve the solubility of a drug in the pressure-sensitive adhesive. It should be appreciated that admixture of a polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines does not alter the polarity of the polyacrylate pressure-sensitive adhesive polymer. Since there are no amino linkages present in the pressure-sensitive adhesive polyacrylate of the present invention, the skilled artisan would not have expected that the mixture of a polyacrylate pressure-sensitive adhesive not comprising amino groups and a polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines pursuant to pending claims 1, 15 and 18 would improve the solubility behavior of the drugs, in particular because U.S. '343 is silent with respect to the presence of drugs such as oestradiol and norethisterone in supersaturated state in the pressure-sensitive adhesive.

The present invention concerns transdermal therapeutic patches comprising the drug(s) in supersaturated state. Supersaturated means that the pressure-sensitive adhesive drug reservoir contains more drug dissolved therein than required for its saturation, i.e. it contains more drug dissolved in it than it should contain in the thermodynamic equilibration. This is a metastable condition at which the dissolved drug can instantly be brought to crystallization by means of inoculating nuclei or shaking. Such particular systems can, if at all, hardly be compared with systems containing a high concentration of drug within its solubilizing capacity and therefore being stable. Therefore, a skilled artisan would not have transferred the teaching of U.S. '343 to supersaturated systems without further inventive activity.

U.S. '711 teaches the kinetic inhibition of the crystallization of a drug by means of the high viscosity of the matrix polymer (col. 6, lines 31-32). Said matrix polymer may be a copolymer based on a aklyl acrylate or methacrylate together with an acrylate comonomer such as dimethylaminoethyl acrylate; dimethylaminoethyl methacrylate, tert-butylaminoethyl acrylate or tert-butalaminoethyl methacrylate (col. 7, line 66 to col. 8, line 8). Hence, the matrix polymer may be a pressures-sensitive adhesive polyacrylate having amino groups. U.S. '711 does not disclose a mixture of a polyacrylate pressure-sensitive adhesive not comprising amino groups and a polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines, nor mentions that such mixtures may have a viscosity that is high enough to kinetically inhibit crystallization of the drug dissolved therein.

The active principle of the crystallization inhibiting amino group-containing polymers in connection with the present invention is not its high viscosity, but the formation of hydrogen bonds between the basic groups of the amino group-containing crystallization inhibitor and the mobile hydrogen atoms of the drug. (This is now recited in claim 15.) This leads to an immobilization of the drug, but not the viscosity of the pressure-sensitive polyacrylate adhesive. Thus, U.S. '711 did not make the transdermal therapeutic patch of the present invention obvious to one skilled in the art at the time the present invention was made.

In view of the aforesaid, it is again repeated that the combined view of U.S. '343 and U.S. '711 might have suggested a pressure-sensitive adhesive polyacrylate copolymer having amino groups and a high viscosity for inhibiting crystallization of supersaturated drug to the skilled artisan. However these two references neither suggest to mix a pressure-sensitive adhesive polyacrylate not having amino groups and another amino group containing polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and

polyglucosamines, nor do they indicate that admixture of an amino group-containing polymer to a pressure-sensitive adhesive polyacrylate without amino groups could inhibit crystallization of supersaturated drug dissolved therein. For this reason, it is requested that the presently claimed transdermal therapeutic patch should be allowed over U.S. '343 and U.S. '711.

WO '227 discloses a transdermal patch for the release of oestradiol and a progesterone agent through the skin. Said transdermal patch comprises a back foil impermeable to the active ingredients, a layer of a pressure-sensitive adhesive matrix, and a release liner. The pressure-sensitive adhesive matrix was chosen from vinylacetate-containing acrylate copolymers (page 5, last paragraph) such as a copolymer obtained by radical polymerization of 2-ethylhexyl acrylate, hydroxyethyl acrylate, vinylacetate and glycidyl methacrylate. The resulting acrylate copolymer is not described as containing nitrogen atoms, and apparently does not contain them.

WO '227 also disclosed that the development of matrix type patches requires solving problems related to the active ingredients, e.g. chemical instability and crystallization (page 4, 2nd paragraph). Furthermore, one skilled in the art becomes aware that oestradiol and/or progesterone tends to form crystals during storage of a transdermal patch (page 7, 1st full paragraph). WO '227 then teaches that the addition of small amounts of octyldodecanol to the base of the adhesive matrix consisting of a vinylacetate-containing acrylate copolymer surprisingly could prevent crystallization of the active ingredient from the supersaturated solution of active ingredient, even after prolonged storage. Thus, WO '227 teaches that octyldodecanol is a crystallization inhibitor for oestradiol and/or a progesterone agent.

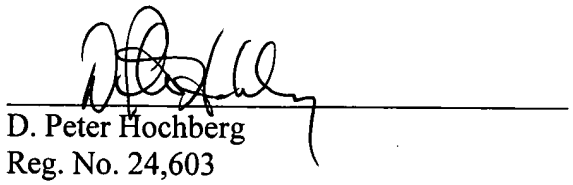
In contradistinction to the crystallization inhibitor pursuant to the present invention, octyldodecanol is neither a polymer nor contains at least one amino group or even a nitrogen. Additional crystallization inhibitors are not mentioned in WO '227. Thus, WO '227 did not suggest

to add an amino group-containing polymer selected from the group of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines to the pressure-sensitive adhesive polyacrylate matrix (to replace octyldodecanol) in order to inhibit or prevent crystallization of the active ingredient(s). Therefore, WO '227 as such did not teach or suggest the present invention of a transdermal therapeutic patch comprising a reservoir comprising a mixture of a polyacrylate pressure-sensitive adhesive not comprising amino groups and a polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines obvious to the skilled artisan.

Likewise, the combined view of U.S. '343 and WO '227 do not render the present invention of a transdermal therapeutic patch comprising a reservoir comprising a mixture of a polyacrylate pressure-sensitive adhesive not comprising amino groups and a polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines obvious to the skilled artisan, because neither or both references teach or even indicate that a mixture of a polyacrylate pressure-sensitive adhesive not comprising amino groups and a polymer selected from the group consisting of polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines, and polyglucosamines can successfully be utilized to inhibit crystallization of active ingredient(s) in a transdermal therapeutic patch. Beyond that, none of the two references U.S. '343 and WO '227 teach that the formation of hydrogen bonds between the basic groups of a crystallization inhibitor and the mobile hydrogen atoms of the oestradiol molecule result in the immobilization of the oestradiol. Thus, the principle the present invention is based on was not disclosed to one skilled in the art prior to the present application. Therefore, inventiveness of the

present invention over the combined disclosure of U.S. '343 and WO '227 should be acknowledged.

Respectfully submitted,



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